REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claims 16-21, 23-29, 32, 37-41, 46-65 and 68-70 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and for the reasons that follow.

Merely for procedural expediency, claims 21 and 32 have been revised to include the clause:

> "...and wherein said chimeric CH2 domain is at least 98% identical to *G1 ac (SEQ ID NO:3) or G4 c (SEQ ID NO:12) as shown in Figure 17.*"

Since the recited sequences correspond to a CH2 sequence (residues 231-340) from human IgG1, IgG2 or IgG4 having said modified amino acids, it is clear that this amendment is fully supported by the disclosure.

Likewise, claims 41 and 55 have been revised to include the clause:

> "...and wherein said chimeric CH2 domain is at least 98% identical to *G1 ab (SEQ ID NO:1) or G2 a (SEQ ID NO:2) as shown in Figure 17.*"

In view of the above, reconsideration is requested.

Claims 16-21, 23-29, 32, 37-39, 41, 46-49 and 50-65 stand rejected under 35 USC 103 as allegedly being obvious over WO94/29351 in light of Greenwood et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Applicants respectfully submit that none of the post-KSR rationales listed as A) – F) on page 7 of the Action are relevant here for the reasons that follow. In particular,

- The results and effects pertaining to the claimed CH2 regions were not "predictable". The unexpectedness of the results themselves are discussed extensively in Applicants' response to the Action dated March 2003 (dated January 26, 2004).
- The technique used (i.e. introduction of the *precise combination of modifications* to achieve the blocks of amino acids recited in the claims) had not previously been used in the art for *any* molecule. Hence, the techniques were not "known", even in a different context.
- There was considerable confusion in the art, i.e., exactly the opposite of "a finite number of identified, predictable solutions". That has been discussed extensively in Applicants' response to the Actions dated July 2, 2002 and March 25, 2003 (dated January 26, 2004) where the pertinent state of the art more generally is discussed.

Applicants remind the Examiner:

> "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." In re Fritch, 23 USPQ2d 1780, 1784 (CAFC 1992).

Rather, as set out in KSR (or 'rationale F') the motivation to make any combination must come from the art, not the claimed invention. Without *ex post facto knowledge of the invention*,

Applicants submit the skilled person would not have been directed towards the *precise combination of modifications* to achieve the blocks of amino acids recited in the claims.

Even based on the combination of WO94/29351 and Greenwood alone Applicants submit there was no suggestion in the art which would have lead the skilled person to the *defined subject matter of the claims* with an expectation of achieving the results obtained by Applicants. This is still more true when considering the state of the art more widely.

Applicants' comments on the invention and the art (including Greenwood) were presented in the response dated January 26, 2004 but are reiterated below for ease of reference. Analysis in that response was in accordance with the test set out in Graham v. John Deere Co, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966) which was a test approved in KSR.

The effect of the invention

Prior to considering the state of the art, Applicants remind the Examiner of the nature of the invention. The effects achieved by the claimed subject matter can be summarized are as follows.

- having lowered complement and other activatory activities such as ADCC (indeed, lower than the progenitor wild-type immunoglobulins in some respects) while,
- minimizing immunogenicity, and
- retaining (at least) FcγRIIb binding.

Further reference to the response dated January 26, 2004 (regarding the unexpectedness of the results) is made hereinafter.

The state of the art

To put the invention in the context of the prior art, it is necessary to consider not just the combination of documents (selected *ex post facto*) by the Examiner, but also other documents concerned with effector functions (e.g. FcR binding; ability to trigger complement and ADCC) and the regions of the IgG which trigger these i.e. WO94/29351 must be considered in the light of the entire state of the art to comply with KSR.

A selection in chronological order:

Duncan and Winter (1988. Nature, 332: 738 – 740) [cited in WO94/29351 on page 41]

This work used scanning mutations of surface residues of murine IgG2b. The ability to lyse NIP-coated sheep RBC in the presence of guinea pig **complement** was found to depend on the presence of certain residues at positions **297** (i.e. presence of carbohydrate), **318, 320 and 322**. Interestingly, the mutation **P331G** was amongst others tested which had no effect.

Tao et al. (1991. J Exp Med, 173: 1025 – 1028) [cited in WO94/29351 on page 41]

These workers used guinea pig **complement** and haptenated sheep red blood cells under conditions where IgG2 was totally inactive. Domain swaps between active IgG3 and inactive IgG2 suggested the CH2 domain as being responsible for the differences in activity between the two antibodies. A second set of experiments used antibodies with hybrid IgG1 and IgG4 constant regions and showed that sequences of IgG1 permitting complement fixation were located mainly in the second half of the CH2 and/or CH3 domain although the first half of the IgG1 constant region was actually three-fold more effective than that of IgG4.

Valim and Lachmann (1991. Clin Exp Immunol, 84: 1 – 8)

This article highlighted that many different factors may affect the ability of a given human immunoglobulin to fix human **complement**. The conclusions were that activation is generally greatest at high epitope density and in conditions of antibody excess or antibody/antigen equivalence and that conditions suitable for activation of the classical pathway do not always allow activation via the alternative pathway.

Sarmay et al. (1992. Mol Immunol, 29: 633 – 639) [cited in WO94/29351 on page 41]

This document was concerned with the interaction between the lower hinge region and FcRs. The paper examined the effects of point mutations at residues 234, 235, 236 or 237 or aglycosylation on the activity of IgG3 in **rosetting and ADCC assays** using either cell lines stimulated to express mainly FcγRI or FcγRII or human K cells expressing FcγRIII. Although (with the possible exception of that at 236) these changes did appear to reduced this activity (the level of reduction varying with mutation and with cell type) a confused picture is painted. The relative levels of FcγRI and FcγRII on the cell lines and their contributions to the assays are unclear, plus there was little correlation between the abilities to form rosettes and mediate ADCC.

Michaelsen et al. (1992. Mol Immunol, 29: 319 – 326)

This paper states that "**complement-mediated lysis and ADCC** have different structural requirements in the Fc region of IgG." (p319), based on their examination of IgG3 hinge mutants. Stepwise reduction of hinge length from 62 to 15 residues, to resemble the hinges of other subclasses, or mutation to be identical to the IgG4 hinge had no effect on ADCC activity with NK/K cells. Complete removal of the hinge reduced ADCC by 100-fold but did not

eliminate it. In contrast, complement-mediated lysis was enhanced with the 15 residue hinge and eliminated by complete removal. Epitope patchiness increased complement-mediated lysis but reduced ADCC.

Dorai et al. (1992. Mol Immunol, 29: 1487 – 1491)

This paper showed that the inter-heavy and light chain disulphide bond pattern also affects **complement- and FcR-mediated effector functions**. The IgG1 heavy chain is unique in forming a disulphide bond with the light chain from a position in the hinge rather than from a point at the N-terminal end of the CH1 domain. When IgG1 was mutated to have the same disulphide bond arrangement as IgG4, its ability to mediate ADCC by human PBMC was effectively abolished, falling at least 106-fold to be less than that of IgG4, and it was 10-fold less efficient at mediating complement-dependent lysis. The authors note that similar properties resulted from the removal of the inter-heavy chain disulphide bond.

Wright and Morrison (1994. J Exp Med, 180: 1087 – 1096)

These authors investigated the effect of changing the nature of the carbohydrate rather than its complete removal. They compared of the activities of IgG1 antibodies produced from wildtype CHO cells and CHO cell line Lec 1, which synthesizes oligomannosyl, truncated sugars not normally found on IgG. Lysis and consumption of guinea pig **complement** was reduced at least 10-fold and binding of human C1q was decreased by altering the carbohydrate. Binding to human FcγRI was reduced about five-fold.

Brekke et al. (1995, Immunol Today, 16: 85 – 90)

This review notes that the hinge, and the flexibility it offers, are not in themselves essential for **complement activation** although they may assist in interaction with multiple

antigen sites. However the inter-heavy chain disulphide bridge **is** necessary, although it still allows activity if repositioned from the hinge to the beginning of the lower hinge region of the CH2 domain.

The authors refer to Duncan & Winter (1988) and their attempt to locate the binding site for C1q on IgG by site-directed mutagenesis. They also note that work swapping sections of domains has shown the C-terminal part of the CH2 domain to be important and that residue 331 is partly, **but only partly**, responsible for the difference between human IgG1 and IgG4.

When non-lytic murine IgG1 was substituted with the lower region or with three individual hinge-proximal loops from lytic IgG2b, the lytic activity was not transferred to it.

On this subject, they finish by stating "Clearly, more work is needed to elucidate which additional residues in the CH2 domain are involved in complement activation." (p 88).

Ward and Ghetie (1995 Therapeutic Immunology, 2: 77 – 94)

This discusses a similar set of factors affecting ability to mediate complement lysis as that covered by Brekke et al.(1995) but also points *inter alia* to residue **237** of the lower hinge region. On the subject of activity via Fc receptors, the authors look at the importance of the lower hinge region (residues 233 - 238) and discuss different mutations in the region which have affected receptor binding. They conclude that this site is recognized by all three classes of FcγR but in a different way such that different residues are important for different receptors.

A E**318**A change in murine IgG2b removed its ability to form rosettes via FcγRII. The authors state that "It is obvious that there are not enough data to claim that the FcγR-binding region of IgG is located in three distinct regions irrespective of the class of FcγR recognized." (p83), indicating that the residues involved in the binding have not been elucidated for all three

classes of FcγR. Aglycosylation also reduces binding to FcγR. In concluding, the authors say "...there is evidence that three sequentially distinct, but spatially close peptide stretches are involved in building both C1q and FcR interaction sites." and "...it will be difficult to genetically engineer an IgG antibody to abolish complement activation whilst retaining FcγR binding." (p 90).

Conclusions on the state of the art

By looking back at the art as it stood prior to the present invention, several issues become apparent. Sometimes-contradictory evidence obtained using numerous different systems and focusing on numerous different possible regions meant that it was not possible to draw general conclusions about effector functions, and IgG constant regions. Indeed, given the complications highlighted by Valim & Lachmann, it is not surprising that groups testing the effects of mutations on complement activity have obtained different results, especially since not all have utilized human complement. To take one example, Brekke *et al.* (in 1995, after WO94/29351 and Greenwood) suggested glycosylation of the CH2 domains was crucial for activation, and the presence of the CH3 domains was also essential for full activity. However, even this apparently straightforward conclusion is complicated by the fact that the ability to bind to C1q was not sufficient for complement activation, since other factors appeared to discriminate between subclasses at the level of complement component C4.

Thus, Applicants submit that it was unclear at the date of invention whether point mutations of the CH2 domain could even be used to finely tune the interactions between IgGs and effector molecules. Even if a point mutation approach was adopted, it was not clear which were the residues to mutate and which amino acids to substitute.

Turning now to WO94/29351 and Greenwood:

WO94/29351

Regarding the Examiner's comments on page 4, final paragraph of the Action, Applicants accept that the WO94/29351 made some changes near the hinge-link region and offer experimental data on the resulting molecule G1/G2L-hinge molecule (in respect of complement fixation).

However, in keeping with KSR, it should be noted that there were quite different options taught in WO94/29351 which would have appeared to one skilled in the art as superior in some respects. Thus, if the data from WO94/29351 was to be used as a starting point from which to design a human constant region with the properties required (see above under "the effect of the invention") it would seem the G4[L235E] might have been chosen in preference to the G1/G2L-hinge, since the former has much lower activity in ADCC (p37, lines 10-12 and figure 16).

Additionally at the start of page 5, the Examiner states:

> 94/29351 publication teaches the C-terminal half of the CH2 domain affect complement Clq binding and exchanging the G1/G2 lower hinge exchange abolished complement fixation (see page 41, lines 6-36, in particular). The publication further suggests that changing IgG1 residues

However, the disclosure cited by the Examiner is part of a summary of separate literature. That literature is reviewed more fully above, and much of it is of-record. The fuller analysis of the experimental results in the art above, and in the documents themselves, shows that it was not possible to draw simple predictable rules connecting the structure and function of the CH2 domain.

Indeed WO94/29351 itself teaches the **opposite** in respect of the "C-terminal half" in terms of experimental results. Thus, the only change made in "the C-terminal half" – mutant G1[K320A] – **did not effect complement lysis** (p41, lines 16-18 and figure 11, Fig 16).

This further illustrates that the art was not simply a group of finite predictable teachings and options, it was in fact contradictory and confusing, even within a single document.

The Examiner comments on page 5:

> The WO 94/29351 publication does not teach the altered antibody having the following residues 327G and 330S in the C-terminus of CH2 from human IgG1 numbered with respect to the EU numbering system.
> However, Greenwood et al teach humanized IgG antibody that binds to CAMPATH-1 (also known as CD52) that has the following 327G, 330S and 331S in the CH2 domain.

As discussed above, the fact that (using the invention as a template) different elements of it can be carefully selected after the fact is not relevant to obviousness. Rather there must be – at least - motivation for combining the references and elements of the references. Applicants here also note that Greenwood et al predated the filing date of WO94/29351. Therefore, if it provided motivation to modify the molecules described therein to obtain superior ones, why was that not done ?

WO94/29351 plus Greenwood et al

In turning to Greenwood et al, the Examiner initially refers to its teaching in respect of complement-mediated lysis i.e.

> col. 2, second paragraph, Figure 5, in particular). However, changing residues Tyr 296 to Phe, the antibody remained as potent as wild-type for complement lysis, indicating that the failure of IgG4 to activate complement is not due to the lack of Tyr in this position, see page 1101, col. 1,

However, given that G1/G2L-hinge molecule of WO94/29351 already showed low FcRI-binding and complement activities, why would the skilled person even be seeking **yet further** mutations for lowering complement-mediated lysis ? In this respect it is a characteristic of the present invention to aim to maintain low immunogenicity, while also balancing the activatory and inhibitory effect functions. Thus, the skilled person, even if motivated to solve this problem (which is itself not a problem discussed in the cited art), would proceed on the basis of keeping changes to a minimum.

Thus, although it is acknowledged that Figure 2a of Greenwood et al suggests that the C-terminal region does indeed have a role in complement-mediated lysis, that problem had already been solved in WO94/29351, so there was not "motivation" to solve it again.

In fact, for completeness, it should be noted that the Y295F mutation did appear to **lower** complement-mediated lysis slightly (Figure 2b; note the displacement of the curve to the right). Therefore, the skilled person, if still concerned with the complement-mediated lysis problem, would have been faced with yet further choices because all of the lower hinge, the middle of the molecule, and the c-terminal region would seem to affect this property.

Additionally, since Greenwood et al states, on page 1099, column 1, line 16-20 that "the critical residues" for ADCC and complement-mediated lysis are in the C-terminal half, why would the skilled person even contemplate combining these with changes in the hinge-link region (cf. above) ? It would seem that one or the other would be enough.

In any case, the examiner goes on, on page 6, to discuss the problem of reducing ADCC:

> 2, Figure 1, DS111/41, Figure 5, in particular). Greenwood et al teach residues which were essential for mediating antibody dependent cellular cytotoxicity (ADCC) were located in the second half of the CH2 domain, see page 1101, col. 2, in particular). Greenwood et al teach

In fact, Figure 3 of Greenwood et al shows that substituting the C-terminal half of the IgG4 CH2 into an IgG1 molecule (including, therefore, the Y295F change) does not reduce ADCC activity to IgG4 levels (c. 20% vs. 10%).

However, if page 1101, column 2 is read in its entirety, including the 2nd paragraph, it can be seen that Greenwood et al cautions against an over-simplistic approach, stating:

> "Effector cells from certain other donors did not behave the same way. In these, the effector cells were able to mediate [ADCC] killing not only through IgG1 but also through the wild-type IgG4 CAMPATH-1 antibodies, as well as any of the hybrid antibodies that were tested."

Considering the discussion on page 102, lines 1-11, Greenwood et al teaches an IgG1 antibody substituted with the C-terminal half of an IgG4 CH2 would be **active** in ADCC in a very significant proportion of individuals since 5 of 8 donors tested exhibited this phenotype.

As discussed below (see "unexpected results") the particular mutants claimed in the present application can, in fact, show lower levels of ADCC than even IgG4 in such cases, but that could not have been predicted from Greenwood et al.

The Examiner concludes the first paragraph on page 6 by saying:

> in particular. Greenwood et al teach the critical residues identified pave the way for future modifications to the natural antibody structure, designed to improve their ability to harness natural effector functions, see page 1104, last paragraph, in particular.

However this paragraph in Greenwood et al must be seen in the context that Greenwood et al is concerned with the opposite aim of the present invention – namely increasing lytic activity. The ultimate aim is to attempt to locate the sites responsible for ADCC/complement lysis, so that multiple copies of the important regions can be incorporated into a recombinant antibody and the effector activity increased (Abstract, lines 10-12).

In terms of blockading target cells (as in the present invention), Greenwood *et al* advocate native IgG4 (see page 1099, last sentence of Introduction – also Figure 3). There is no discussion of whether or indeed how it could be improved for this purpose.

The Examiner goes on to say on page 6

> terminus of CH2 domain of human IgG1 is unable to activate complement, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the WO 94/29351 publication with the teachings of Greenwood et al to arrive at the claimed invention wherein the binding molecule is capable of binding to any target molecule and

However this position is not consistent with the facts above:

- There was no clear teaching in the art as to which residues were responsible for which activity, or whether in fact multiple regions contributed in different ways to different activities.
- Since the G1/G2L-hinge molecule of WO94/29351 already showed very low FcRI-binding and complement activities, there was no motivation for the skilled person to make further changes to it for lowering complement-mediated lysis.
- Since Greenwood et al teaches the IgG4 residues 296F, 327G, 330S and 331S would not eliminate ADCC activity for a significant proportion of patients there would be no motivation to include 327G, 330S and 331S as additional substitutions in the G1/G2L-hinge molecule.
- Greenwood et al teaches that native IgG4 should be used as a cellular blockade. This expressly contradicts the notion that the skilled person on reading WO94/29351 and Greenwood et al would be lead towards the presently claimed multiple-mutants for that purpose (i.e. the purpose of the present invention).

- Greenwood et al (the 'secondary' document) predates WO94/29351. If it was "obvious" to the skilled person that the Greenwood et al teaching could be combined with the WO94/29351 teaching to somehow improve it, why did the WO94/29351 inventors not do that suggest that in their patent application ?

The Examiner goes on to state:

> 330S and 331S numbered with respect to the EU numbering system of Kabat. Although the prior art does not disclose the altered antibody effector domain is capable of binding to FcγRIIb, the prior art antibodies would have had the inherent property of binding to FcγRIIb to the extent claimed because of the same structure which has the following blocks of amino acids 223P, 234V, 235A, no residue at 236, 327G, 330S and 331S. One of skill in the art would choose from

However, Applicants submit this comment is unfounded for 2 reasons:

- The claims do not embrace the "prior art antibodies" – therefore whether they inherently bound FcγRIIb is not relevant to the claimed subject matter.
- It is settled law that obviousness can not be predicated on inherency.

There was no teaching in the cited documents about how FcγRIIb binding could be maintained when other binding activities (ADCC, complement-dependent lysis) were being eliminated or reduced. Meeting that challenge was yet another reason why the claimed subject matter is non-obvious.

The Examiner later continues:

> 234V, 235A, no residue at 236, 327G, 330S and 331S. One of skill in the art would choose from this finite number of identified residues with a reasonable expectation of success absent of any objective evidence of unexpected results. One having ordinary skill in the art would have been

However, Applicants submit this comment is unfounded for several reasons:

- It is not accepted that there was motivation in the art to even begin combining the different documents with their different purposes and teachings.
- As set out above, there was in fact a great deal of ambiguity in the art about which residues played a role in which activity. Thus one or ordinary skill would not have proceeded with any reasonable expectation of success of maintaining or eliminating the combinations of receptor binding activity.

Additionally, the results of Applicants are indeed unexpected. For ease of reference, Applicants here reiterate the comments made in the response dated January 26, 2004 (pages 43-44).

Unexpected results

Even if the skilled person had an idea about which regions to modify and how to do it to (which is denied) they would not have "reasonably expected" that multiple effector functions could be reconciled in the manner achieved by the present invention. The position that the Examiner has taken is that it was believed in the art that the effector functions can simply be independently manipulated and combined in any IgG background by simple substitutions. However, this position is not supported by the literature.

Considering the present application, in respect of FcγRI binding, Figures 2 and 3 show that mutations Δb and Δc of IgG1 (+/-Δa) and IgG4 produced mutants with very low or undetectable binding to this receptor. The binding was at least 1000-fold lower than that of IgG4 - a result could scarcely have been predicted from Chappel (or record) where the binding of wild-type IgG4 itself was practically undetectable.

The activation of monocytes in response to antibody-sensitised RBC is zero when using IgG2 or several of the mutant IgG including G1Δb and G2Δa (Figure 4). However, in experiments where the inactive antibodies were used to try to inhibit the activity of IgG1, IgG2 was four-fold **less efficient** than the mutant antibodies (Figure 5).

Figure 10a shows an example of RBC ADCC where IgG2 and IgG4 mediate significant levels of lysis. However, substitution of IgG2 residues into IgG4 (G4Δb), IgG4 residues into IgG2 (G2Δa) or both IgG2 and IgG4 residues into IgG1 (G1Δab) effectively eliminates killing. The activity of these mutants is at least 100-fold less than that of IgG2 and IgG4 and they are more effective than IgG2 and IgG4 in blocking the activity of active antibody (Figures 11a and 12).

The results in Figure 10a are in sharp contrast to Figure 16 in WO94/29351. In Figure 10a not only is IgG1 is highly active but IgG2 and IgG4 antibodies also mediate significant amounts of ADCC. However the preferred mutant antibodies of the invention show no ADCC activity. Such a complete loss of activity in otherwise active 'parent' IgGs could certainly not be predicted from WO94/29351, where donor cells were used in which IgG2 itself showed no activity at all.

Although less clear, Figure 9 similarly shows that with CAMPATH ADCC, IgG2 and IgG4 are again more active than the presently claimed mutants.

In binding to FcγRIIa 131H (Figure 13a), IgG1 and IgG2 are equally active. Taking residues from the inactive IgG4 and substituting them into IgG1 and IgG2 (G1Δa and G2Δa) reduces binding by about four-fold. However taking residues from the active IgG2 and substituting them into IgG1 reduces binding by factors of 10 (G1Δc) or 50 (G1Δb).

Thus, Applicants showed, *inter* alia:

- That IgG mutants with less effector activity than *either* of the parent antibodies could be created (see above) and indeed that substitutions from an "active" subclass could be more efficient at reducing activity than those from an inactive subclass (see e.g. Figure 7, which shows that G1Δb and G1Δc, derived from the active IgG2, nevertheless reduced complement activity in IgG1 to background levels and thus were more effective than the Δa change, based on the "inactive" IgG4).
- That a relatively high level of binding to Fcγ RIIb could be retained while effecting a much greater reduction in binding to FcγγRIIa, notwithstanding that the receptors are so similar in structure.

In view of the foregoing, it is clearly improper to simply assert that there was a "reasonable expectation" of arriving at the invention.

KSR

As noted at the outset, Applicants submit there is nothing in KSR or the Guidelines which should lead to rejection of the presently claimed invention as obvious.

Considering points A)-F):

A), B) The results and effects pertaining to the claimed CH2 regions were not "predictable" both due to the confusion in the art, and the unexpectedness of the results obtained. Likewise, a decade of frequently conflicting publications before the priority date showed that there was no "simple substitution" to make which the skilled person could have predicted the outcome of in terms of the various receptor binding activities.

C), D) The technique used (i.e. introduction of the *precise combination of modifications* to achieve the blocks of amino acids recited in the claims) had not previously been used in the art for *any* molecule. Hence the techniques were not "known", even in a different context.

E) There was considerable confusion in the art, i.e., exactly the opposite of "a finite number of identified, predictable solutions" with a "reasonable expectation of success".

F) As set out above, whether for reasons of complement-dependent lysis or ADCC, there was no motivation for the skilled person to seek to combine particular substitutions from WO94/2935, or Greenwood et al, for the purposes of the present invention. More likely, one of ordinary skill in the art would have used the mutants taught in either, or indeed IgG4 as expressly taught in Greenwood et al. The properties of the presently claimed mutants (including the degree of reduction of the activatory responses, and maintenance of the inhibitory response) could not be predicted from the teachings of those documents, or the art more generally.

Furthermore, the Examiner states on page 8:

> invention was made. Claims 21 and 32 are included in this rejection because chimeric CH2 domain having a glycine at position 236 instead of no residue is an obvious variation of teachings of the Greenwood et al who stated that IgG1 at position 236 has a glycine (G) residue, and the glycine residue at position 236 is conserved among IgG1, IgG2 IgG3 and IgG4, see page 1103, Figure 5, in particular. Claims 16-17 are included in this rejection because both references teach

For completeness, Applicants note that Figure 5 in Greenwood et al is in fact in error. Gly236 is not conserved between all IgG sub-classess because it is not present in IgG2 (see present application Figure 17).

The Examiner goes on to say:

> methodologies to produce the claimed nucleic acid from the protein. Claims 24-26 and 58-60 are included in this rejection

> because substituting residues 327G, 330S and 331S from IgG4 into IgG1 within the CH2 domain of the effector retains the effector function of IgG4, i.e. binds to FcγRIIb receptors since only Fc of the IgG4 binds FcγRIIb receptors. The binding of such

This comment is not understood, and the Examiner is respectfully requested to provide support for the comment that only the "Fc of IgG4 binds FcγRIIb" or withdraw this rejection.

In conclusion, in the present case, it is a mis-characterization of the prior art to say there was ". . . a finite number of identified, predictable solutions." On the contrary, there were many suggestions in the art about the possible structure-activity relationships for the residues of the CH2 domain and the stimulatory and inhibitory activities of the molecules, and no indication of whether such stimulatory and inhibitory activities could even be independently manipulated.

Further, there was no clear teaching in the art to even identify immunoglobulins in which the stimulatory and inhibitory activities were independently manipulated. The desirability and feasibility of that was an insight of Applicants. Absent that, there was no reason to even modify the existing molecules (or indeed IgG4) rather than simply utilize them.

Therefore, Applicants submit that the cited documents do not support a rejection based on obviousness. Reconsideration is requested.

Claims 68-70 stand rejected under 35 USC 103 as allegedly being obvious over WO 94/29351 in view of Greenwood et al and Griffin et al. Griffin et al adds nothing that would have cured the fundamental failings of WO 94/29351 and Greenwood et al. Accordingly, Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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